REMARKS

Claims 1-23 are pending in this application. Claims 18-21 have been withdrawn, leaving claims 1-17, 22, and 23 remaining. Claims 1 and 23 have been amended.

The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Basis for the claim amendments is found on page 8, line 1, to page 30, line 16; in claims 1-23 as originally filed; and elsewhere throughout the specification and claims. Accordingly, entry of the amendments is respectfully requested.

1. Objections to the Drawings

The Office Action objects to the drawings for the reasons stated in the accompanying PTO Form 948: improper marks; views not separately labeled; poor line quality; and improper reference character size.

Applicants thank the Examiner for his helpful comments. Applicants have amended the drawings to correct those matters stated as the grounds for objection. Corrected Figures 1-7 are attached hereto.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objections to the drawings.

2. Sequence Rules Compliance

The Office Action objects to the Specification for non-compliance with the sequence listing requirements for nucleotide and/or amino acid sequences set forth in 37 CFR §§1.821(a)(1) and (a)(2) because it lacks any submission of a computer readable form sequence listing, a paper copy for the specification, a statement under 37 CFR §§1.821(f) and (g), and SEQ ID Nos cited along with each sequence in the specification. In particular, the Office Action refers to, for example, the Zif268 sequence on page 18 in Table 1 of the instant specification; the sequences in Table 2A on page 21; and the sequences in Table 3 on page 24, Table 4 on page 28.

Applicants thank the Examiner for his helpful comments in correcting the sequence non-compliance. Applicants have amended the Specification to correct those matters stated as the grounds for objection. Applicants hereby assert under 37 CFR §§1.821(f) and (g) that the information recorded in computer readable form on the disk submitted with this Response is identical to the written sequence listing.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection to the Specification for non-compliance with the sequence listing requirements.

3. Objections to Claim Numbering

The Office Action objects that the numbering of claims is not in accordance with 37 CFR 1.126, in particular because claim 23 has been misnumbered as claim 32. The Office Action notes that this claim has been renumbered, and Applicants have made this change in the claim set presented herein.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection to the claim numbering.

4. Rejection of Claims 1-17, 22, and 23 under 35 U.S.C. §101 and §112, first paragraph

The Office Action rejects claims 1-17, 22, and 23 under 35 U.S.C. §101 and §112, first paragraph because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility, and thus is not enabled because one skilled in the art clearly would not know how to use the claimed invention, for the following reasons:

> The claimed subject matter is not supported by a specific, substantial, and credible utility because the disclosed uses are generally applicable to broad classes of this subject matter. In addition, further characterization of the claimed subject matter would be required to identify or reasonably confirm a "real world" use. The examiner does not find an adequate nexus between the evidence of record and the asserted properties of the claimed subject matter.
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> Applicants should explicitly identify a specific, substantial, and credible utility for the claimed invention and establish a probative relation between any

evidence of record and the originally disclosed properties of the claimed invention.

The claimed invention lacks either specific or substantial utility. Reconsideration of the instant claims reveals that a method is set forth for the prediction of an amino acid sequence which is constructed via evaluation of solvent accessibility without any specific or substantial utility for the predicted protein or peptide. In part a of claim 1 a 3D structure is set provided but without any specificity as to a connection to a utility for the structure. That is, there is no required substrate binding activity set forth. Alternatively, there is no recognition of a binding entity present as a claimed limitation nor set forth in the instant specification. Additionally, the solvent accessibility which is utilized in the claimed method to be compatible with the solvent accessibility at each position is not directed to a protein or peptide utility. Thus, a generic utility is apparently meant for the protein or peptide being predicted as to its amino acid sequence. A generic utility is not specific as required by 35 U.S.C. § 101. There is also a lack of a substantial utility as there is no substantial utility defined or even asserted for the predicted protein or peptide sequence as a result of performance of the methods as claimed either for enzyme activity or some type of binding or recognition activity such as present in proteins or peptides which act as receptors, for example, or possibly peptides which bind to receptors in order to produce some type of biological response for said binding. It is noted that claim 2 includes a native protein as an option for providing the 3D structure for part (a) of claim 1. Nothing specific or substantial is therein set forth as to such a native protein, but rather a general or generic protein is set forth without further limitation regarding utility thereof thus additionally supporting this determination of a lack of specific or substantial utility. It may be postulated that the solvent accessibility is somehow related to protein or peptide utility in step c of instant claim 1. This, however, is not asserted as defining a utility for the practice of step c in the instant specification nor in the claims such that the solvent accessibility results in some type of protein or peptide utility. It is acknowledged that one aspect of a protein's or peptide's function includes solvent accessibility for binding activity, but that such solvent accessibility per se

lacks specificity as to what binding then occurs for entities which have access via solvent accessibility. Is hydrogen bonding then utilized via such accessibility? Is there ionic bonding? Are other types of interaction/bonding then utilized for protein or peptide function or activity? At best solvent accessibility provides access but does not produce whatever interactions or bond availability thus results in a protein or peptide activity or function. Thus, the utility of predicting an amino acid sequence for a protein or peptide as instantly claimed lacks specificity or substantiality as to utility without some nexus to protein or peptide activity or binding reactions which will result in specific and substantial utility. It is noted that no well established utility has been asserted or is known for generic amino acid sequence prediction without some utility for the resultant protein or peptide. It is also noted that, in the absence of a well known utility, a utility must be substantiated which has the combination of specific, substantial, and credible utility. Since the instant invention as disclosed lacks either specific or substantial utility, the credibility is not required to be assessed. That being stated, it is acknowledged that protein or peptide design per se is deemed a credible utility for proteins or peptides with some function or activity which has both a specific and substantial use.

* * *

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

> The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.
>
> In the practice of the instant claims, the construction of a "reduced" virtual representation is required for step b of claim 1, and all dependent claims due to their dependence directly or indirectly from claim 1. This construction of a "reduced" virtual representation is essential subject matter for the performance of this step in the instantly claimed method. Consideration of the instant disclosure reveals that a publication is apparently incorporated by reference to set forth the details of such a "reduced" virtual representation on page 9, lines 4-6. It is noted that the specification on page 9, lines 7-27, sets forth some concepts in this virtual representation but never discloses with any significant details as to how this is performed in the claimed invention regarding coordinates as provided firstly in step a of instant claim 1. Thus, reliance on said printed publication on page 9, lines 4-6, for this practice is apparent thus also making this printed publication essential subject matter for the practice of the instant claims. The incorporation of essential subject matter via incorporation by reference to a printed publication is improper as also explained in the following paragraph and thus lacking in enablement.
>
> The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the Applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See in re Hawkins, 486 F.2d 569,179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579,179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577,179 USPQ 167 (CCPA 1973).

Applicants respectfully traverse the rejection for lack of utility, for the following reasons.

The two full paragraphs on page 15 of the specification provide a utility for the sequences of the invention. In particular, a sequence may be obtained having biological activity similar to a native protein, but more stable than the native protein.

Additional disclosed utilities of the invention are the following:

Therapeutic proteins. Therapeutically relevant proteins, such as immunoglobulins, hormones or insulin, suffer from very poor stability once injected to patients. Their short half-life in the blood limits their application requiring frequent injections, often possible only at a setting of a hospital. A re-designed version of the same therapeutically relevant protein that will improve the stability of the protein and increase its duration in the blood may offer a great improvement. Improving the quality of life of people that depend of this therapies (reducing the number of injections per-day) and potentially allowing treatment at home or day-clinics instead of hospitals. This will also significantly reduce the cost of such treatments to the healthcare system.

Another utility for more stable versions of known therapeutic proteins is the possibility to increase their proteolytic stability to the level that they could be administered orally (or nasally). Currently these treatments have to be given using injections because they cannot survive the enzymatic reactions in the gut. An

oral administration of such treatments, e.g., oral insulin, is a target that is being actively sought after by many pharmaceutical companies with clear benefit to patients.

Biotechnology Utilities. Today's biotechnology industry often uses microorganism as manufacturing platforms. Millions of bacteria, altered to express a specific protein of interest, are grown in fermentation tanks and then harvested for the protein that they produce. Such processes can often benefit from high temperature but the sensitivity of the bacteria to these conditions prevents optimizing the fermentation conditions. By introducing into these bacteria re-designed genes, which express proteins that are thermally more stable, the sensitivity of the bacteria to elevated temperatures will reduce and the efficiency of the biotechnological process improved.

Designing Novel Therapeutic Proteins. The scientific community is gradually becoming aware of the major role that protein-protein interactions play in regulating biological processes. This awareness is being manifested by the willingness to explore novel proteins as therapies. The new technology is optimal for designing new therapeutic proteins. For example, chemokines, which are small natural proteins that are part of the immune system, have a generic role of attaching to antigens and signaling their whereabouts. Using our technology, by optimizing the stability of the protein-protein interface instead of the protein's core, it may be

possible to invent specific tailor-made chemokine-like therapeutic proteins that will attach specifically to a certain viral antigens. This may constitute new anti-viral treatments both against standard ailments as well as in the event of bioterrorist attack. See page 15, line 28 of the specification: "Another application of the invention disclosed herein may be the generation of a library of small stable protein elements that can be later assembled in various ways to design a sequence for a novel larger protein with a desired 3D structure."

Building Blocks for Nanotechnology. The goal of the emerging world of nanotechnology is to build nanometer-size devices, i.e. devices which are molecule size. To allow that vision to materialize it is important to construct nanometer-size building-blocks. Namely, molecules that can be used as building blocks to construct larger devices. These building blocks must have two properties: (1) they have to be stable in themselves, and (2) they should be adhesive so that they can stick to one another. The new technology can be used to invent such building blocks from small proteins, stabilizing the protein building-block's core and simultaneously design an optimal protein-protein interface between two such building blocks. See page 15, line 29 to page 16, line 3 of the specification: "Yet further, the method of the present invention may be applicable for optimizing the novel larger protein obtained thus ensuring that the peptides from which it was

constructed indeed fit the structure."

Novel Therapeutic Peptides. As discussed above, proteins have significant drawbacks as therapeutic agents. One way to overcome the stability problem of therapeutic proteins is to derive a small peptide that has similar (or better) activity. Such small peptides are often more stable than the parent protein. A problem with this approach is that the small peptide fragment often loses its potential activity because it fails to adopt the desired 3D structure of the equivalent region in the parent protein. It is thus essential to take into account the 3D structure when deriving smaller peptide versions of therapeutic proteins. The new technology is designed to enable such a process and ensure that the derived therapeutic peptide, which should have better pharmacological properties, will be stable enough in its therapeutically relevant conformation. A possible example may be for example a low-molecular weight oral version of insulin for diabetes patients.

Applicants respectfully submit that the above information fully addresses the Examiner's request to specify a utility. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the utility rejection of claims 1-17, 22, and 23.

Applicants respectfully traverse the rejection for lack of enablement, for the following reasons.

As Applicants understand the enablement rejection, the Examiner requests that the method disclosed in the Herzyk, et al. reference be described in more detail. Applicants have amended the Application to insert a description of Herzyk at after line 12 on page 9.

In the alternate, if the Examiner feels that it is necessary to properly enable the inventive subject matter, the entire Herzyk reference can be added to the specification. In that instance, Applicants respectfully request that the Examiner contact Applicants' counsel to discuss amending the Specification to insert the complete text of the Herzyk reference, without the need for a further Office Action.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-17, 22, and 23 for lack of enablement.

5. Rejection of Claims 1-17, 22, and 23 under 35 U.S.C. §112, first paragraph

The Office Action rejects claims 1-17, 22, and 23 under 35 U.S.C. §112, first paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for the following reasons:

> In claim 1, step d, the "compatible" limitation causes this claim and those dependent therefrom to be vague and indefinite as there is no instant definition of what the metes and bounds of this limitation are. Does compatible indicate that the solvent accessibility is the same? Does it indicate that it is similar without defining a spatial similarity limit? Such comparative limitations are vague and indefinite unless some definition of what the comparison limits are. Clarification is requested via clearer claim wording.
>
> The antecedent basis for "each position" in claim 1, step c is vague and indefinite and causes claims dependent from claim 1 to also contain this unclarity. Does this indicate each amino acid position in the backbone of step a given some putative protein or peptide such as listed in claim 2 to start with? The claim does not clearly and concisely point to amino acids as defining "each position" in step c. Could the positions for "each position" be defined by solvent accessibility surfaces in the "undefined" starting backbone of step a? Clarification via clearer claim wording is requested.
>
> In claim 1, step d, a conflict exists between the first 2 lines of this step and the last 2 lines of step d. In the first line a random amino acid sequence is assigned, but then in the last 2 lines non-random amino acid selection apparently is set forth via a solvent accessibility requirement. These random vs. non-random practices conflict. Clarification via clearer claim wording is requested.
>
> In claim 1, part iv, a determination is set forth for accepting or rejecting a mutation but without any definition of the metes and bounds of what determines the acceptance or rejection. Clarification via clearer claim wording is requested.

Applicants thank the Examiner for his helpful comments. Applicants have amended claim 1 to address those matters stated as the grounds for the rejection.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-17, 22, and 23.

6. Rejection of Claims 1-5, 9-17, 22, and 23 under 35 U.S.C. §102(e)

The Office Action rejects claims 1-5, 9-17, 22, and 23 under 35 U.S.C. 102(b) as being anticipated by Dahiyat et al., (Protein Science, 1996, Vol. 5, pages 895-903). As the basis for this rejection, the Office Action states:

> This rejection is maintained and reiterated from the previous office action, mailed 8/9/02, and claim 23 is added as being directed to computer practices which are suggested as also well known for such computers for automation as noted in the title of Dahiyat et al., for example. Applicants argue firstly that the reference does not utilize a "reduced" virtual representation set. In response the abstract of the reference discloses steric complementarity using a van der Waals potential. This is a disclosure of a type of reduced representation of the rotamers as described in the reference over other representations such as utilizing electron orbitals or other complex quantum mechanical representations contrary to the arguments of applicants. Applicants further argue that the reference does not utilize solvent accessibility as a design parameter. In response the previous office action clearly set forth the designing of protein from surface area burial, buried atoms, hydrophobic and hydrophilic positions which are solvent accessibility determinations again contrary to the arguments of applicants. Applicants then argue a lack of Monte-Carlo search algorithms in the reference. Again in response the usage of Monte-Carlo algorithms for sequence searching was noted in said previous office action on page 897 of the reference contrary to applicants' argument. In summary all of applicants' arguments are non-persuasive as being contrary to the factual basis for this rejection.

Applicants respectfully traverse this rejection on the basis that the present amendment to Claim 1 overcomes the lack of novelty objection in view of the Dahiyat reference, because the "reduced

representation" as claimed is restricted to a "reduced representation" as disclosed in the Herzyk reference. In this representation, at least one of the amino acids is represented by two or more spheres, where in the Dahiyat reference, a representation is used in which each amino acid is represented by a single sphere. Using two or more spheres to represent an amino acid endows the representation with flexibility, whereas there is obviously not flexibility in an amino acid represented by a single sphere. To constitute anticipation under 35 U.S.C. § 102, all material elements of a claim must be formed in one prior art source. In re Marshall, 577 F.2d 301, 198 USPQ 344 (CCPA 1978); In re Kalm, 378 F.2d 959, 154 USPQ 10 (CCPA 1967). Claim 1 amended as above is clearly novel over the Dahiyat reference, which fails to teach the claimed subject matter.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw this rejection.

7. Rejection of Claims 1, 3-15 under 35 U.S.C. §103(a)

The Office Action rejects claims 1-17, 22, and 23 under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (Protein Science, 1996, Vol. 5, pages 895-903), and further in view of Hurley et al. (JMB Vol. 224, 1992, pages 1143-1159). As the basis for this rejection, the Office Action states:

> This rejection is reiterated and maintained from the previous office action, mailed 8/9/02, but additionally applied to claims 1-5, 9-17, 22, and 23 as the embodiments in claims 6-8 as previously rejected are deemed embodiments within claims 1-5, 9-17, 22, and 23 as being recited in claims 6-8. Applicants argue the lacking descriptions in Dahiyat et al. These arguments directed to Dahiyat et al. have been responded to above as being non-persuasive and are reiterated here as being equally non-persuasive and responded to as noted above. Applicants additionally argue that Hurley et al. does not remedy the lacking descriptions in Dahiyat et al. In response, Dahiyat does not lack what applicants allege and thus Hurley et al. does not need to remedy that for which no remedy is required. Applicants then argue that the energy evaluation in Hurley et al. is limited to particular residues and also utilizes a different energy evaluation method than that as instantly claimed. In response, the instant claims are not limited as to what portion of the sequence is evaluated as to energy scoring, either buried or solvent accessible thus making this argument be directed to a instant claim limitation which is not present in the instant claims. Further, the instant claims do not limit the particular energy scoring methodology and thus that utilized in Hurley et al. is deemed to be within that of the generic energy scoring practice of the instant claims. Thus, the arguments of applicants are non-persuasive.

Applicants respectfully traverse this rejection. To establish a *prima facie* case, the PTO must satisfy three requirements. First, the prior art reference relied upon must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Second, the prior art, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596,

1598 (Fed. Cir. 1988). Lastly, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991).

As noted above, in the claimed subject matter, at least one of the amino acids is represented by two or more spheres, where in the Dahiyat reference, a representation is used in which each amino acid is represented by a single sphere. Using two or more spheres to represent an amino acid endows the representation with flexibility, whereas there is obviously not flexibility in an amino acid represented by a single sphere. For the reasons discussed above, claim 1 as amended has an additional element not disclosed in the prior art, and is thus non-obvious over Dahiyat in view of Hurley.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

8. Informalities

The Office Action objects to the claims for the following informalities:

> Claim 1 contains improper internal periods. The periods, for example, in the part "a." or "b.", etc. designation in claim 1 are improper. Claim 23 also contains improper periods. Periods are only permitted

within a claim in abbreviations and at the end. Applicants are suggested to replace the part designation periods with parentheses, for example.

Applicants thank the Examiner for his helpful comments. Applicants have amended the claims to address those matters stated as the grounds for objection.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw these objections.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to have utility, be enabled, be novel, and be patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of remaining claims 1-77, 22, and 23, and allow all pending claims presented herein for reconsideration. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she/he has any questions or comments.

Respectfully submitted,

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